AMENDMENTS TO THE DRAWINGS

Please replace the drawing sheets containing Figures 2, 3B, 4B, 7A, 14, 15, 20, 27, 28 and 29 with the replacement sheets provided herewith.

REMARKS

On July 1, 2004, Applicants filed a Preliminary Amendment requesting that claims 81-110 and claims 140-212 be canceled. After reviewing the previously issued Restriction Requirement and the instant Office Action, it appears that the Preliminary Amendment was not entered. If this is correct, Applicants now cancel, without prejudice or disclaimer, claims 81-110 and claims 140-212 in accordance with the request made in the July 1, 2004 Preliminary Amendment.

Currently claims 1, 3, 4, 7 and 19 are presented for examination. Claim 2 is canceled and claims 5, 6, 8-18, 20-80 and 111-139 are withdrawn without prejudice or disclaimer. Applicants reserve their right to pursue the subject matter of any withdrawn and/or canceled claims in one or more continuing applications.

Claims 1, 3 and 19 are amended. Support for the amendments to claims 1, 3 and 19 can be found in claim 2, at Example 39, Example 45, Example 47 and elsewhere throughout the specification and claims as originally filed.

After careful review of the instant Office Action, Applicants respectfully traverse the rejection of claims 1, 3, 4, 7 and 19.

References Submitted in Information Disclosure Statements

Applicants would like to thank the Examiner for thoroughly reviewing the references in each of the Information Disclosure Statement (IDS) submissions. Applicants are providing herewith an updated equivalent of Form PTO/SB/08 re-listing certain references that were incompletely listed in the IDS submission received at the PTO on November 22, 2004 (particularly, GenBank Accession Number AB012668, dated September 8, 1998 and GenBank Accession Number NP_002980, dated March 24, 1999). Additionally, the PTO/SB/08 equivalent lists certain references that the Examiner asserts were not included in either the IDS submission received at the PTO on November 22, 2004 or the IDS submission received at the PTO on March 11, 2005. Copies of each of these references are also provided. Applicants believe that no fee is due since the PTO acknowledges receipt of each of the references provided with the original IDS submissions (see enclosed copies of returned postcards).

Drawings

The Examiner objects to drawings 2, 3B, 4B, 7A, 14, 15, 20, 27, 28 and 29 as being too dark. Applicants enclose replacement sheets herewith, which contain lighter versions of drawings 2, 3B, 4B, 7A, 14, 15, 20, 27, 28 and 29. In view of these replacement sheets, Applicants respectfully request that the Examiner withdraw the instant objection to drawings 2, 3B, 4B, 7A, 14, 15, 20, 27, 28 and 29.

Specification and Sequence Listing

The Examiner objects to the specification and/or the Sequence Listing as allegedly not including appropriate sequence designations and/or sequences corresponding to the sequences set forth in Figures 18A and 18B. Applicants respectfully submit that the sequences set forth in Figures 18A and 18B are present in the Sequence Listing as SEQ ID NOs: 140-159. Furthermore, the section of the Brief Description of the Drawings which references Figures 18A and 18B includes SEQ ID NOs: for each of the sequences appearing in Figure 18A and 18B. As such, Applicants respectfully request that the Examiner withdraw the instant objection to the specification and/or the Sequence Listing.

Rejection of Claims 1-4, 7 and 19 under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejects claims 1-4, 7 and 19 under 35 U.S.C. § 112, first paragraph as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner asserts that the specification (1) "fails to provide any description for a gene associated with any inflammatory disease which is further regulated by THAP1;" (2) "does not teach whether any THAP protein has a transcriptional repressor or activator such that an artisan could use THAP or any 'biologically active fragment thereof' and monitor transcriptional activity;" and (3) does not enable an artisan to expect that several conserved amino acids amongst proteins would necessarily have the same structure and biological activity between proteins."

Applicants believe that each of the originally-filed claims is more than adequately supported by the instant specification. However, in order to expedite the issuance of this

application, Applicants have amended claim 1 to contain the limitation recited in claim 2. In view of this amendment, claim 2 has been canceled. The remainder of Applicants' remarks regarding the written description requirement are therefore directed to amended claims 1, 3, 4 and original claims 7 and 19.

Applicants have carefully considered the Examiner's rejection of claims 1-4, 7 and 19, which is alleged to be based on the written description requirement of the first paragraph of section 112 of the Patent Act. Applicants do not agree that requirements of that section have been appropriately applied to these claims. However, Applicants will address the three issues raised by the Examiner.

First, the Examiner alleges that the specification fails to provide any description for a gene associated with any inflammatory disease which is further regulated by THAP1. As an initial matter, Applicants note that claims 1, 3, 4 and 7 do not recite that the gene is involved in inflammation. Thus, this rejection seems to be directed to claim 19. In any case, Applicants would like to direct the Examiner's attention to Example 47 which describes in Tables 3A and 3B at least 120 genes, which have their expression modulated in response to THAP1 bound to SLC. This list includes at least three genes, BIRC5/survivin, BCLA2 and RHAMM/HMMR, whose products are known to be involved in inflammation (see Altznauer, et al. (2004) *J. Exp. Med.* **199**:1343-1354; Kloosterboer et al. (2005) *Blood* **106**:3955-3957; and Nedvetzki et al. (2004) *PNAS*: **101**:18081-6, respectively – enclosed herewith for the Examiner's convenience). Also, the Examiner should take note of the text at page 343, lines 1-5, which states that modulation of expression occurs in response to THAP1-SLC complexes as well as in response to THAP1 alone. This fact is further supported by the evidence at page 321, lines 1-27 and Table 2A, which shows that both survivin and HMMR expression is modulated in response to THAP1 alone. Accordingly the specification supports claims 1, 3, 4, 7 and 19.

Second, the Examiner alleges that the specification does not teach whether any THAP protein has a transcriptional repressor or activator such that an artisan could use THAP or any biologically active fragment thereof and monitor transcriptional activity. Applicants respectfully disagree. However, claim 1 has been amended to relate to " a THAP1 polypeptide or a biologically active fragment thereof." As discussed above, Examples 39, 45 and 47 provide clear

support for the involvement of THAP1 in transcriptional modulation. Accordingly the specification supports claims 1, 3, 4, 7 and 19.

Finally, the Examiner alleges that the specification does not enable an artisan to expect that several conserved amino acids amongst proteins would necessarily have the same structure and biological activity between proteins. Again, Applicants disagree. It is a well known fact that proteins having conserved domains have the same general function (for example, the heme-binding domain of hemoglobin and myoglobin, the catalytic triad of serine proteases, etc.). However, claim 1 has been amended to relate to " a THAP1 polypeptide or a biologically active fragment thereof." As discussed above, Examples 39, 45 and 47 provide clear support for the involvement of THAP1 in transcriptional modulation. Accordingly the specification supports claims 1, 3, 4, 7 and 19.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 3, 4, 7 and 19 under the written description requirement of 35 U.S.C. § 112, first paragraph.

Rejection of claims 1-4, 7 and 19 under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejects claims 1-4, 7 and 19 under 35 U.S.C. § 112, first paragraph as allegedly encompassing subject matter that is not enabled by the specification. In particular, the Examiner asserts that a skilled artisan would not be able to practice the invention with any THAP-family polypeptide. Furthermore, the Examiner asserts that Applicants have not shown any relationship between the modulation of genes involved in inflammation, THAP1 and the THRE response element.

Applicants respectfully submit that claims 1, 3, 4, 7 and 19 are enabled. First, Applicants reiterate their remarks in response to the written description rejection as they apply to the instant enablement rejection. Next, Applicants respectfully submit that enablement of the instant claims does not require a showing of a relationship between the modulation of genes involved in inflammation, THAP1 and the THRE response element. Applicants would like to point out that, claim 1 is drawn to a method of modulating expression of a THAP1 responsive gene by modulating the interaction of a THAP1 polypeptide or a biologically active fragment thereof with a nucleic acid. To practice the invention as set forth in claim 1, a skilled artisan does not need to

know whether transcription modulation is by direct activation or repression or whether it occurs indirectly, for example, by initiation of a signal transduction cascade. Furthermore, a skilled artisan does not need to know or understand any specific sequence or structural relationship with respect to either THAP1 or the nucleic acid to which it binds. All that is required is the knowledge that THAP1 binds to a nucleic acid and modulates transcription of certain classes of genes. Applicants have provided numerous working examples which demonstrate the transcriptional modulatory activity of THAP1. Additionally, Applicants have set out in detail examples of routine methods by which a skilled artisan can determine which genes are modulated either by THAP1 alone or by THAP1 complexed with a chemokine.

In addition to enabling independent claim 1, the specification enables each claim dependent thereon. Claim 19, which further specifies that the THAP1-responsive gene encodes a polypeptide involved in inflammatory disease, depends from claim 1. The instant specification provides at least three examples of modulating the activity of a THAP-responsive gene encoding a polypeptide involved in inflammatory disease (see Examples 47 and 45 as discussed above). In view of the guidance provided by these examples, a skilled artisan could easily identify other genes involved in inflammatory disease that are modulated by THAP1.

Claim 3, which depends from claim 1, states that the nucleic acid is a THAP-responsive promoter. Claim 4 states that the THAP-responsive promoter comprises a THAP responsive element. Both THAP responsive promoters and THAP responsive elements are defined in the specification at page 148, line 13 to 150, line 2 as follows:

> As used herein, "THAP responsive promoter" means, a promoter comprising one or more THAP responsive elements. THAP responsive promoters also include promoters that are indirectly regulated by THAP. For example, a THAP responsive element may be present as an upstream enhancer sequence, the presence of which, activates transcription at the downstream promoter. In another nonlimiting example, a first promoter may be modulated by a polypeptide that is encoded by a gene under the control of a second promoter having a THAP responsive element, however, the first promoter does not comprise a THAP responsive element. In such a case, the activity of the first promoter is indirectly

responsive to THAP because transcription is modulated by the polypeptide encoded by the second promoter which is responsive to THAP.

As used herein, "THAP responsive elements" include, but are not limited to, nucleic acids which comprise one or more of the following nucleotide consensus sequences. The first THAP responsive element consensus sequence comprises the nucleotide sequences GGGCAA or TGGCAA organized as direct repeats with approximately a 5 nucleotide spacing (DR-5 motifs). For example, one consensus sequence is GGGCAAnnnnnTGGCAA (SEQ ID NO: 149). Although GGGCAA and TGGCAA sequences constitute a typical THAP domain DNA binding site (THAP responsive element), GGGCAT, GGGCAG and TGGCAG sequences are also DNA target sequences recognized by the THAP DNA-binding domain. Additionally, a second THAP responsive element consensus sequence comprises the nucleotide sequences TTGCCA or GGGCAA organized as everted repeats with 11 nucleotide spacing (ER-11 motifs). For example, one consensus sequence is TTGCCAnnnnnnnnnnnGGGCAA (SEQ ID NO: 159). Although TTGCCA and GGGCAA sequences constitute a typical THAP responsive element, CTGCCA is also recognized.

Another THAP responsive element is the THRE consensus sequence which is illustrated in Figure 24 (SEQ ID NO: 306). In some embodiments of the present invention, THRE is a preferential recognition motif for monomeric THAP-family polypeptides or biologically active fragments thereof. In some embodiments, THRE is preferentially recognized by the THAP1 monomer. Alternatively, in some embodiments, the DR-5 and/or the ER-11 motif is preferentially recognized by a dimer or a multimer of a THAP-family polypeptide or biologically active fragments thereof. In some embodiments, the THAP dimers or multimers comprise THAP1.

A THAP responsive element can comprise either a single type of consensus nucleotide sequence, multiple types of consensus sequences. For example, a THAP responsive element can comprise one, two, three, four, five or more than five DR-5 consensus sequences. Similarly, a THAP responsive

element can comprise one, two, three, four, five or more than five ER-11 consensus sequences. In another example, a THAP responsive element can comprise one, two, three, four, five or more than five THRE consensus sequences. In addition, a THAP responsive element can comprise a mixture of two, three, four, five or more than five DR-5, ER-11 and THRE consensus sequences. Furthermore, any of the aforementioned THAP responsive elements can comprise one or more variants of DR-5, ER-11 or THRE consensus sequences or variants of some or all of DR-5, ER-11 or THRE consensus sequences.

It will be appreciated that other minor nucleotide sequence variations can occur in THAP responsive element consensus sequences which do not substantially affect the binding of the THAP domain to the THAP responsive element. For example, a THAP responsive element can comprise a nucleic acid having at least 99%, at least 98%, at least 97%, at least 96%, at least 95, at least 94%, at least 93%, at least 92%, at least 91%, at least 90, at least 89%, at least 88%, at least 87%, at least 86%, at least 85, at least 84%, at least 83%, at least 82%, at least 81%, at least 80, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, or at least 50% nucleotide sequence identity to a consensus sequence for DR-5, ER-11 or THRE.

It is clear that the specification provides examples of genes modulated by THAP1 that include THAP-responsive promoters and THAP-responsive elements. In particular, Example 46 describes the localization of a DR5-type element in the survivin gene and a THRE element in the USP16 gene. It is also clear that a skilled artisan would be able to inspect the promoter sequences of other THAP-modulated genes to identify THAP-responsive promoters and/or THAP-responsive elements without undue experimentation.

Claim 7, which depends from claim 4, states that the THAP-responsive element is THRE. As discussed above in connection with claims 3 and 4, the specification provides an example of a THAP-modulated gene having at THRE element. Based on the teachings of the specification, a skilled artisan would be able to inspect the promoter sequences of other THAP-modulated genes

to identify THAP-responsive promoters and/or THAP-responsive elements without undue experimentation.

Finally, Applicants also do not agree that the specification lacks enablement for the use of any THAP-family polypeptide in methods of modulating transcription. However, Applicants believe that this aspect of the enablement rejection has been sufficiently addressed by the amendment to claim 1.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 3, 4, 7 and 19 under the enablement requirement of 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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